Practitioner's Docket No. 701586-050174-DIV *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Adam Lerner		
Serial No.:	10/060,759	Group:	1614
Filed:	January 30, 2002	Examiner:	James D. Anderson
Confirmation No.:	8480	Customer No.:	50607
For:	COMPOSITIONS AND METHODS FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA		

2nd LERNER DECLARATION UNDER 37 C.F.R. 1.132

I, Adam Lerner, M.D., pursuant to 37 C.F.R. § 1.132, hereby declare that:

1. I am an Associate Professor of Medicine in the Section of Hematology/Oncology at Boston Medical Center, Boston University. A true copy of my CV is attached hereto as Exhibit A.
2. I am the sole inventor of the above-described application.
3. I have been advised that the Examiner in the October 31, 2007 Office Action has contended that "inhibition of Type 4 to a greater extent that Type 1 and/or Type 2 phosphodiesterases is not within the meaning of an inhibitor that *specifically* inhibits Type 4 adenosine monophosphate diesterases" (emphasis in original). I have also been advised that the Examiner further alleged that "[o]nly two specific inhibitors of Type 4 adenosine monophosphate diesterases are disclosed in the specification" and that "no other specific inhibitor of Type 4 adenosine monophosphate diesterases are contemplated or described."
4. I have been further advised that the Examiner also contended that "the specification provides no direction or guidance for determining the particular administration regimes (e.g., dosages, timing, administration routes, etc.) necessary to treat CLL with the broad genus of compounds contemplated by the claims, particularly in humans." I have also been advised that the Examiner further contended that "because of known unpredictability of the art... and in the absence of experimental evidence commensurate

in scope with the claims, the skilled artisan would not accept the assertion that full scope of the instantly claimed genus could be predictably used as a treatment for CLL in human patients..."

5. I respectfully disagree with these assertions by the Examiner for the following reasons.

6. With respect to the Examiner's allegations regarding the lack of described or contemplated specific PDE4 inhibitors I respectfully disagree for the following reasons.

7. The specification at page 1, lines 4 – 8 and again page 2, lines 11 – 20, specifically teaches that the invention pertains to treatment of chronic lymphocyte leukemia (CLL) with pharmaceutical compositions comprising "an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase". At page 3, a specific example of such an inhibitor, rolipram, is exemplified. Page 4, lines 6 – 13 provides further guidance about what "an inhibitor that specifically inhibits Type 4 cyclic adenosine monophase phosphodiesterase" is. This is further discussed at pages 6 – 7. At page 7, two specific type 4 inhibitors are described with cites thereto and they are distinguished from "theophylline", which is described as inducing apoptosis in CLL cells, "but is not a specific Type 4 inhibitor". See also the examples at pages 19 – 23, that described experiments with what was then the best specific PDE4 inhibitor, namely, rolipram. I also confirmed these results using the inhibitor called XX5 also known as Ro20-174 (as discussed in my first Declaration). In addition, I cited publications by Schwabe et al. (1976) and Sheppard et al. (1972) wherein additional description of these specific PDE4 inhibitors can be found. And these results were contrasted with the results obtained with theophylline.

8. Prior to the filing date, September 24, 1998, the term "specific PDE4 inhibitor" was well known: A number of other specific PDE4 inhibitors were well known to a skilled artisan. For example, compounds RP73401, LAS31025, SB207499, and CDP840, CP80633, CP77059BRL61063, denbufylline, and MNS949 were all known to the skilled artisan as specific PDE4 inhibitors (see, e.g., review by Teixeira et al. Trends in Pharm. Sci. 18:164-71, 1997, attached herewith as Exhibit B, and Cooper et al. British Journal of Pharmacology, 126:1863-1871, 1999, attached herewith as Exhibit C). It has further been well known that different forms of PDEs can be differentially inhibited with pharmacological agents (see, e.g., Lerner and Epstein, J Biochem 393:21-41, 2006, attached herewith as Exhibit G).

9. I taught that the class of such specific PDE4 inhibitors could be used and exemplified it with two examples. Accordingly, in view of my discovery that one can use specific PDE4 inhibitors to treat chronic lymphocytic leukemia (CLL) a skilled artisan would have known exactly the class of specific PDE4 inhibitors that one can use.

10. As a result, based both on the specification and the general knowledge in the at prior to September 24, 1998 a skilled artisan would have known what kind of inhibitors were specific PDE4 inhibitors and what were not.

11. With respect to the Examiner's allegations regarding absence of experimental evidence which allegedly would not allow the skilled artisan to accept that full scope of the genus could be predictably used as a treatment for CLL in human patients, I respectfully disagree for the following reasons.

12. I stated in my first Declaration that rolipram, which was used in the examples described in the specification, is referred to as a **prototypical** PDE4 inhibitor. This means that people in the field view results obtained by using it as representative for results obtained using other specific PDE4 inhibitors. Table 2 of Teixeira et al. describes in detail a number of well known PDE4 inhibitors, and confirms their functional similarity, namely, that they all specifically inhibit PDE4. (Teixeira et al., Trends in Pharm. Sci. 18:164-71, 1997, Exhibit B).

13. Because of the functional similarity of the PDE4 inhibitors, I was confident that once I had demonstrated that rolipram was an efficacious treatment for CLL, other specific PDE4 inhibitors would also be useful to treat CLL. I tested another specific PDE4 inhibitor Ro20-174. My studies with that PDE4 inhibitor, Ro20-174, confirmed this finding. The data for both of these PDE4 inhibitors are included in the specification.

14. My results have been further confirmed by my own studies of the treatment of CLL with a third PDE4 inhibitor. One set of my experiments is represented in the graph attached herewith as Exhibit F. In this experiment, apoptosis was analyzed in CLL cells exposed to increasing concentrations of a PDE4 inhibitor in the presence or absence of 40 micromolar forskolin.

15. I obtained the PDE4 inhibitor used in this experiment under a confidentiality agreement with its manufacturer, a pharmaceutical company. Thus, I am not able to disclose its name or structure. I can certify that this compound is a highly selective inhibitor for PDE4, which is different from, but functionally similar to rolipram and Ro20-174.

16. I have also co-authored an article confirming that two additional PDE4 inhibitors work about as effectively as rolipram (Meyers et al. Phosphodiesterase 4 inhibitors augment levels of glucocorticoid receptor in B cell chronic lymphocytic leukemia but not in normal circulating hematopoietic cells, Clin Cancer Res. 2007 Aug 15;13(16):4920-7 attached herewith as Exhibit D). These studies confirm what we already described in the specification that the broad class of specific PDE4 inhibitors is effective in treatment of CLL.

17. We have confirmed these results with 5 different specific PDE4 inhibitors.

18. Thus, for the above reasons, I respectfully disagree with the Examiner's statement that the experimental evidence based on the two examples described in the specification, namely rolipram and Ro20-174, would not have allowed the skilled artisan to accept that all PDE4 inhibitors could be predictably used as a treatment for CLL in human patients.

19. I have also been advised that the Examiner contended that "the specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration, etc.) necessary to treat CLL."

20. I respectfully disagree.

21. A skilled medical doctor who has experience in treating CLL, like myself, will take into consideration all the factors as indicated in the specification in section C from page 7 to 11 for adjusting dosages, timing and administration routes for any new medicines, including the broad group of PDE4 inhibiting agents.

22. Moreover, the skilled artisan would look to the well known uses of rolipram as anti-inflammatory agents and as antidepressants, referred to, for example on page 24, lines 8-14 to determine suitable dosage ranges. Further, the skilled artisan would also look into the efficacy of any new PDE4 inhibitor compared to any known inhibitor, such as rolipram, and determine useful dosage ranges from such information.

23. Accordingly, I disagree with the Examiner that the skilled artisan would not have enough direction and guidance for determining administration regimes to treat CLL using specific PDE4 inhibitors according to the description provided in the present application.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 24, 2008

Date

Adam Lerner